

TRANSFORMATIONS ON DIAZAQUINONE ADDUCTS

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Abstract - Chemical transformations performed on diazaquinone adducts prepared by the authors research group, and stereochemical features of derivatives synthesized from them, are reviewed.

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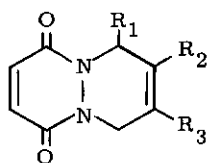
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1. INTRODUCTION

During the past few years our group has been developing a wide research program concerning the reactivity of diazaquinones as dienophiles in (4+2) cycloaddition reactions. Results obtained have been collected in a recently published review on the chemistry of diazaquinones¹. In the course of these investigations different types of diazapolycyclic adducts have been synthesized. Since we are trying to obtain compounds referable to non-heterocyclic analogs of known biological activity, the adequate substituents must be incorporated to the adducts formed in the cycloaddition, in order to approach them to the desired structures as much as possible.

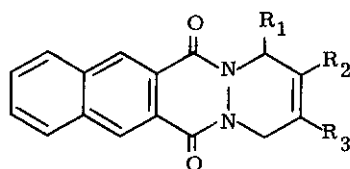
Therefore, their reactivity and stereochemistry have been studied from this point of view. The variety of results observed in some of the reactions performed, so much as the great number of new diazapolycyclic derivatives described, are the main reasons which led us to accomplish this article, exclusively centred on the chemical behaviour and stereochemical features of the new diazaquinone adducts prepared in our laboratories and their derivatives.

All the adducts whose transformations are reviewed here have been obtained by Diels-Alder cycloaddition reactions between pyridazine-3,6-dione (Ia-d, V-VII, XIV), phthalazine-1,4-dione (IIa-h, VIII, IX), 5-hydroxy phthalazine-1,4-dione (IVa), 5-chloro phthalazine-1,4-dione (IVb), 1,2,4-triazolidine-3,5-dione (X, XIa-b) or 4-phenyl-4-chloropyrazolidine-3,5-dione (XII, XIII) (all of them prepared "in situ" through the oxidation of the corresponding cyclic hydrazides with lead tetraacetate² or tert-butyl hypochlorite³, due to their unstability), and a wide variety of dienes. Their syntheses are described in references accompanying the respective depicted structures.



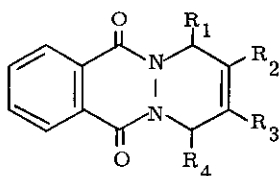
I

- a: $R_1 = R_3 = \text{Me}$, $R_2 = \text{H}$ (Ref. 4)
 b: $R_1 = R_2 = \text{Me}$; $R_3 = \text{H}$ (Ref. 4)
 c: $R_1 = R_3 = \text{H}$; $R_2 = \text{Me}$ (Ref. 5, 6)
 d: $R_1 = \text{H}$; $R_2 = R_3 = \text{Me}$ (Ref. 3, 6)
 e: $R_1 = R_2 = R_3 = \text{H}$ (Ref. 3)



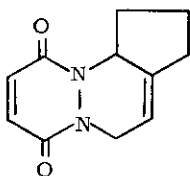
III

- a: $R_1 = R_2 = R_3 = \text{H}$ (Ref. 9)
 b: $R_1 = \text{Me}$, $R_2 = R_3 = \text{H}$ (Ref. 4)
 c: $R_1 = R_3 = \text{H}$; $R_2 = \text{Me}$ (Ref. 10)
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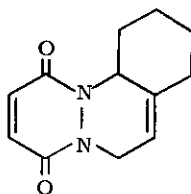


II

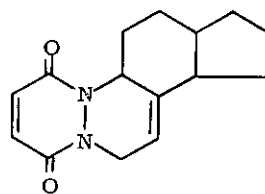
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 c: $R_1 = R_2 = R_3 = R_4 = \text{H}$ (Ref. 2, 3)
 d: $R_1 = R_3 = R_4 = \text{H}$; $R_2 = \text{Me}$ (Ref. 5)
 e: $R_1 = R_4 = \text{H}$; $R_2 = R_3 = \text{Me}$ (Ref. 3)
 f: $R_1 = \text{OAc}$; $R_2 = R_3 = R_4 = \text{H}$ (Ref. 7)
 g: $R_1 = \text{Me}$; $R_2 = R_3 = R_4 = \text{H}$ (Ref. 8)
 h: $R_1 = R_4 = \text{Me}$; $R_2 = R_3 = \text{H}$ (Ref. 8)



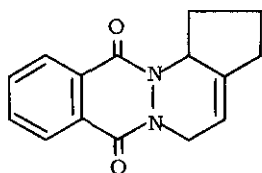
V (Ref. 11)



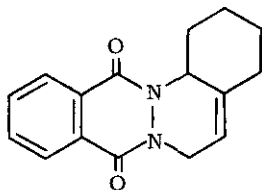
VI (Ref. 11)



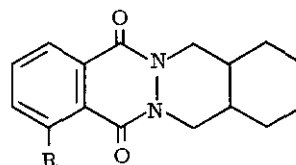
VII (Ref. 11)



VIII (Ref. 11)



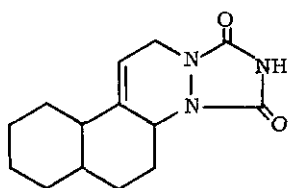
IX (Ref. 11)



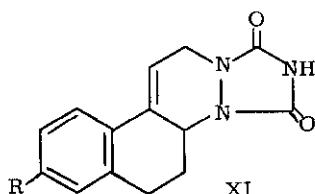
IV

a: R = OH (Ref. 10)

b: R = Cl (Ref. 10)

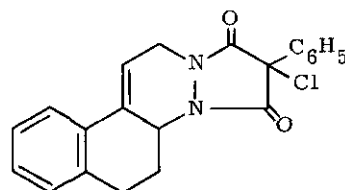


X (Ref. 12)

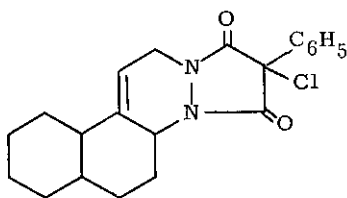


XI

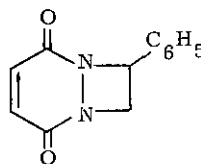
a: R = H (Ref. 12)

b: R = OCH₃ (Ref. 12)

XII

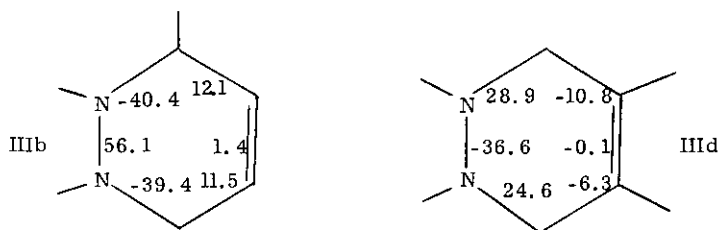


XIII (Ref. 12)



XIV (Ref. 13)

The configurational and conformational characteristics shown by some of these adducts have been studied by means of X-ray diffraction and NMR techniques. In adducts of the types II and III, the atoms of the diazaquinone ring, including the attached oxygens, are almost coplanar, and the degree of puckering is low. The conformation of this ring can be described as a distorted envelope^{14, 15}. Both nitrogen atoms exhibit bond angles in accordance with an intermediate character between sp^2 and sp^3 hybridizations. The terminal tetrahydropyridazine ring can be described as a distorted half-chair, but the degree of deviation from the "pure" half-chair form depends on the position of the substituents in the ring. The presence of a methyl group attached to C₁ in IIIb is responsible for a consistent deviation of the C₁ atom from the planes of the benzo and central rings and, consequently, the torsion angles of the terminal ring in this compound are larger than those of the same ring in adduct IIId, where the planarity is more pronounced¹⁶. This fact causes the N-C₁ bond length to be larger in IIIb than in IIId, and it could provide an explanation for the easy cleavage of this bond in some reactions of adduct derivatives substituted at the C₁ position. The torsion angles found for this ring in IIIb and IIId are shown in scheme 1 for comparison.



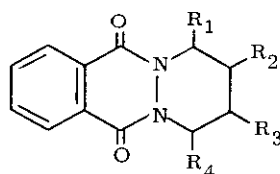
Scheme 1

The solute conformations deduced from NMR evidence correlate well with the solid state conformations established by X-ray studies. However, some kind of conformational equilibrium has been proposed for adducts of the types II, III and IV in solution at room temperature^{17,18}. This hypothesis is mainly supported by the NMR equivalence found between axial and equatorial protons in the heterocyclic rings. The rigid character of the residual portion of the molecule suggests that the equilibrium should take place through nitrogen inversion, as it is usual in piperidazine derivatives¹⁹⁻²¹.

2. REDUCTION REACTIONS

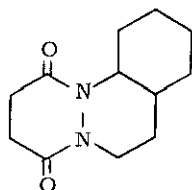
Many of the adducts synthesized have been hydrogenated over palladium on charcoal in ethanol solution. The reaction usually takes place in an almost quantitative manner, and the hydrogenated compounds XV-XXIV have been described. In adducts formed from pyridazine-3,6-dione, simultaneous hydrogen addition to both double bonds occurs⁸.

Hydrogenolysis of the carbon-chlorine linkage with loss of the chlorine atom has been observed during the hydrogenation of the double bond in the 13,14-diaza steroids XII and XIII, to give XXIII and XXIV, respectively¹².

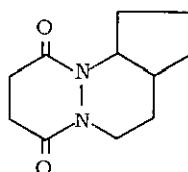


XV (Ref. 8)

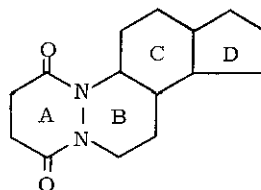
- a: $R_1 = R_2 = \text{Me}$, $R_3 = R_4 = \text{H}$
- b: $R_1 = \text{Me}$, $R_2 = R_3 = R_4$
- c: $R_1 = R_3 = \text{Me}$; $R_2 = R_4 = \text{H}$
- d: $R_1 = R_4 = \text{Me}$; $R_2 = R_3 = \text{H}$
- e: $R_1 = R_3 = R_4 = \text{H}$; $R_2 = \text{Me}$
- f: $R_1 = R_4 = \text{H}$; $R_2 = R_3 = \text{Me}$



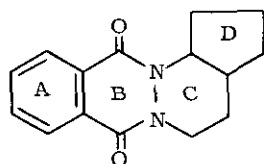
XVI (Ref. 11)



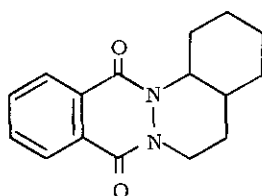
XVII (Ref. 11)



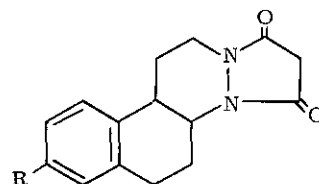
XVIII (Ref. 11)



XIX (Ref. 11)



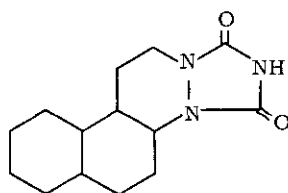
XX (Ref. 11)



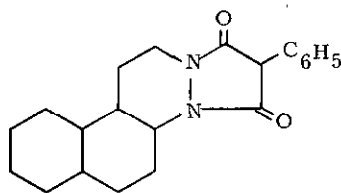
XXI (Ref. 12)

a: R = H

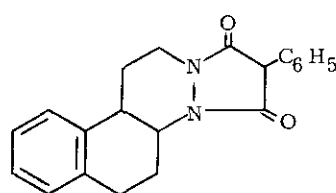
b: R = OMe



XXII (Ref. 12)



XXIII (Ref. 12)

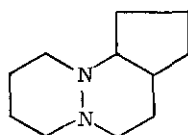


XXIV (Ref. 12)

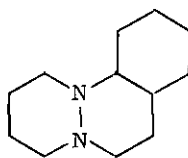
By studying the NMR spectra of compounds XVI-XX, a cis character has been assigned to the junction between rings B and C in XVI-XVIII, or C and D in XIX-XX²². This assignment is supported by the chemical shift differences and coupling constants measured for the three protons of ring B (or C) adjoining the nitrogen atoms. Two of them appear at a much higher field than the other, this difference being only justified if they are equatorial and located in the neighbourhood of the deshielding plane of the C=O group. The appearance of an axial-axial coupling constant in the signal of the third proton confirms its axial assignment. Therefore, the methinic proton adjoining to nitrogen must necessarily be an equatorial one.

On the other hand, the equivalence shown by the four hydrogens of ring A in XVI-XVIII suggests that some kind of rapid interconversion equilibrium should occur, enhanced by the interchange in the type of fusion of rings A and B.

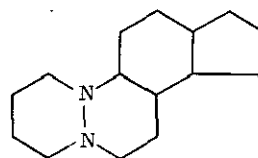
Reaction of the hydrogenated adducts with lithium aluminium hydride in tetrahydrofuran/ether leads to the reduction of the C=O groups. Compounds XXV-XXIX have been obtained^{11, 12}. All these tetrasubstituted hydrazines are unstable liquids, which rapidly decompose on contact with the atmosphere. Due to this instability it is convenient to convert them to suitable solid derivatives, such as hydrochlorides or picrates, before handling.



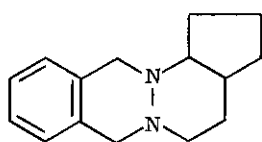
XXV



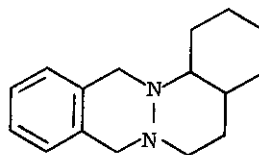
XXVI



XXVII

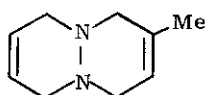


XXVIII

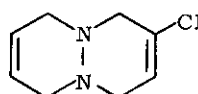


XXIX

Direct reduction of adducts with lithium aluminium hydride has also been reported. Compounds XXX and XXXI have been obtained in that way from the cycloaddition products of pyridazine-3,6-dione with isoprene and 2-chlorobutadiene²³.



XXX

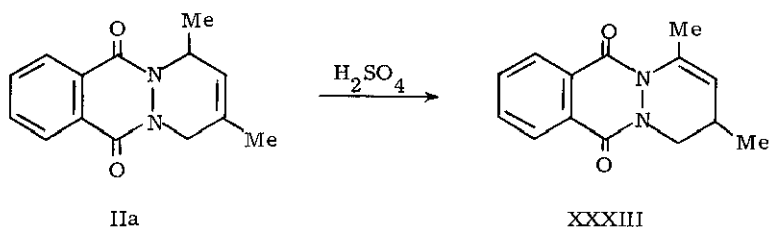
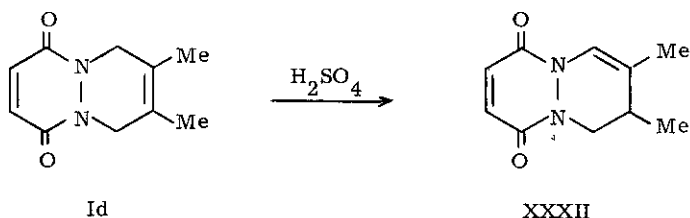


XXXI

3. BEHAVIOUR IN THE PRESENCE OF STRONG ACIDS

3.1 Isomerization of the double bond

When the diazaquinone adducts are treated with concentrated sulphuric acid at 50-60° for several hours, the double bond formed in the cycloaddition is isomerized to the more conjugated 1,2-position. For example, adducts Id and IIa afford the corresponding isomers XXXII and XXXIII in 40 and 95% yields respectively^{6, 24}.

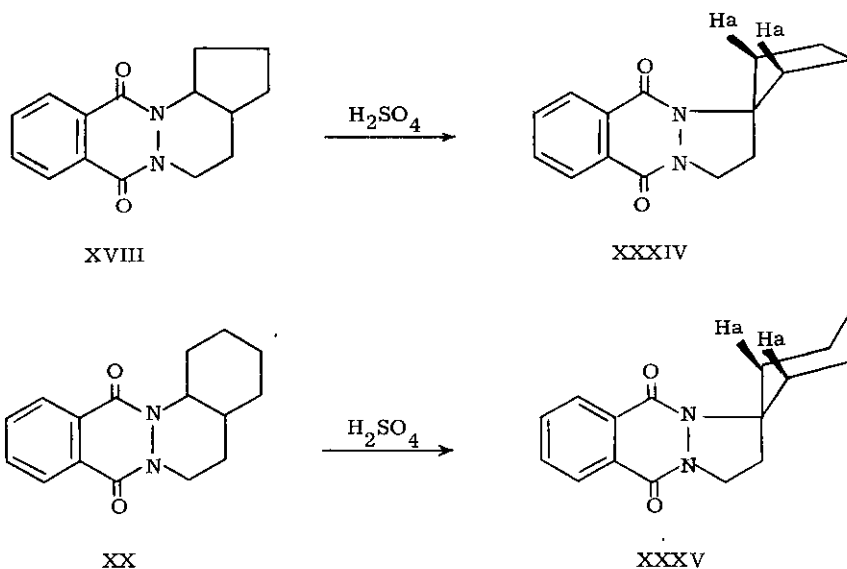


However, this rearrangement only takes place when methyl groups are attached to the double bond and stabilize the intermediate carbonium ion that must be formed in the protonation step. Adducts lacking this kind of substitution are recovered unchanged after the reaction or, in some cases, undergo ring opening, according to the type of substitution in the tetrahydropyridazine ring²⁴.

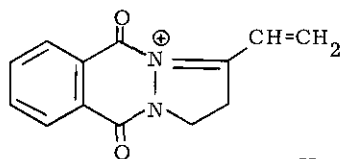
The isomerization products are good starting compounds for the introduction of a variety of substituents in positions 1 and 2 of the terminal ring moiety. Work is now in progress on the study of their configuration and reactivity²⁵.

3.2 Isomerization of hydrogenated adducts

Much interest presents the action of sulphuric acid on derivatives of the cycloaddition adducts in which the double bond formed in the Diels-Alder reaction has been hydrogenated. When the hydrogenated adducts of phthalazine-1,4-dione with 1-vinylcyclohexene (XX) and 1-vinylcyclopentene (XVIII) are treated with concentrated sulphuric acid at 100°C for a half hour, an isomerization occurs to give the spiro compounds XXXIV and XXXV respectively, by contraction of ring C²⁶. These new spiranic structures have been assigned on the basis of their NMR and mass spectra. The deshielding influence of the nearby carbonyl group over the two axial cyclohexanic protons nearest to the spiranic carbon differentiates these protons from the others in the NMR spectra, and allows to assign the position of the rest of the hydrogens. The mass spectra

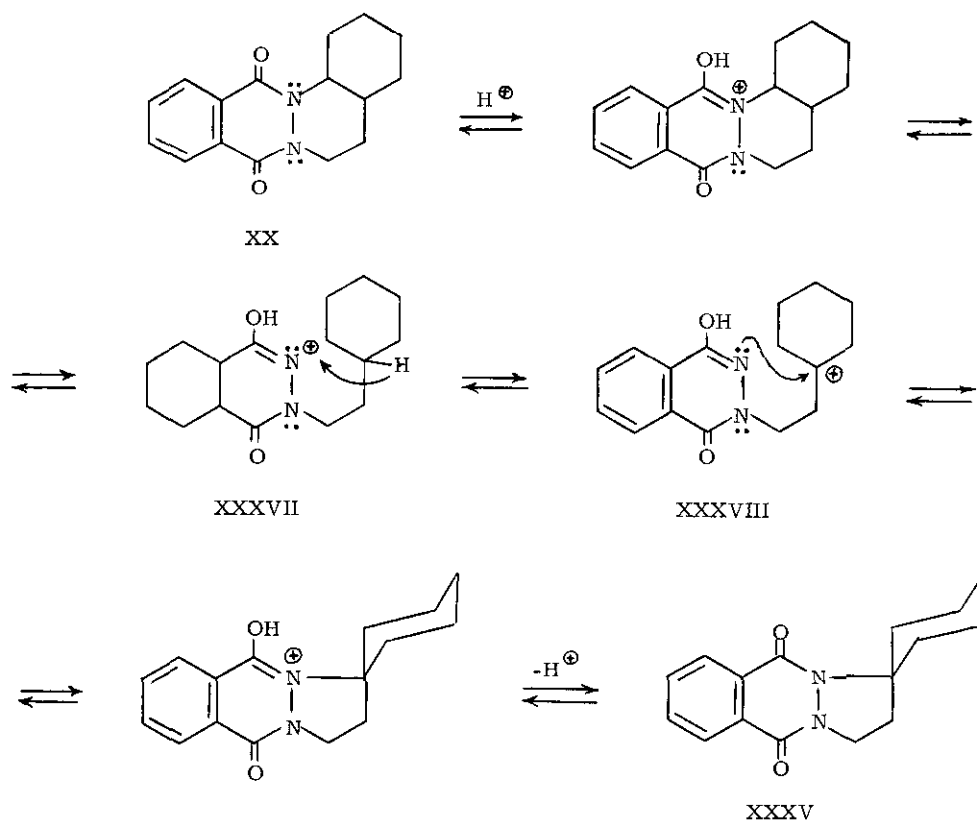


are very useful in the confirmation of the proposed structures, because of the appearance of XXXVI as one of the main fragments in both molecules.



XXXVI

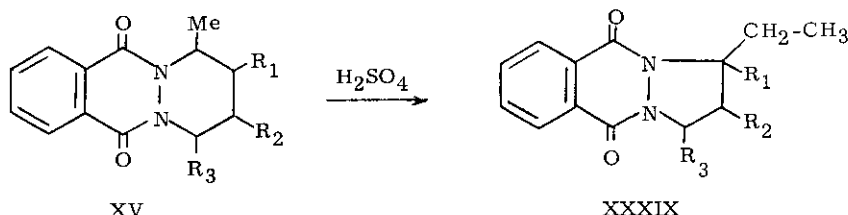
An explanation has been proposed for this isomerization on the basis of an ionic mechanism. Thus, in the case of XX, protonation in the strong acidic medium leads to the secondary carbonium ion XXXVII, which is isomerized to the more stable tertiary carbonium ion XXXVIII. Further cyclization of XXXVIII leads to the spiranic structure XXXV (scheme 2).



Scheme 2

A similar behaviour has been observed in the hydrogenated adducts obtained from the reaction between phthalazine-1, 4-dione and various methyl substituted 1, 3-butadienes. Compounds XVa-d react with sulphuric acid to give the corresponding 1, 2-phthaloyl-3-ethylpirazolidine derivatives XXXIXa-d²⁶

These rearrangements are supposed to occur via the same mechanism proposed for



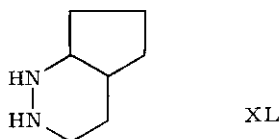
- a: $\text{R}_1 = \text{Me}, \text{R}_2 = \text{R}_3 = \text{H}$
 b: $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{H}$
 c: $\text{R}_1 = \text{R}_3 = \text{H}; \text{R}_2 = \text{Me}$
 d: $\text{R}_1 = \text{R}_2 = \text{H}; \text{R}_3 = \text{Me}$

the formation of XXXIV and XXXV. The only difference is that in compounds XXXIXb-d the initially formed secondary carbonium ion is isomerized to another secondary ion, and not to a tertiary one, as happened in the mechanism shown above.

It must be pointed out that all these reactions always involve the presence of a substituent attached to the carbon atom adjacent to nitrogen. This feature appears as a necessary condition for the isomerization. Thus, when the hydrogenated adducts of phthalazine-1,4-dione with 2-methyl- (XVe) or 2,3-dimethylbutadiene (XVf) are treated with sulphuric acid in the same conditions as above, no isomerization can be observed, and the starting products are recovered unchanged. In both cases, the first carbonium ion formed should be a more energetic primary one and, therefore, the proposed mechanism is not favored.

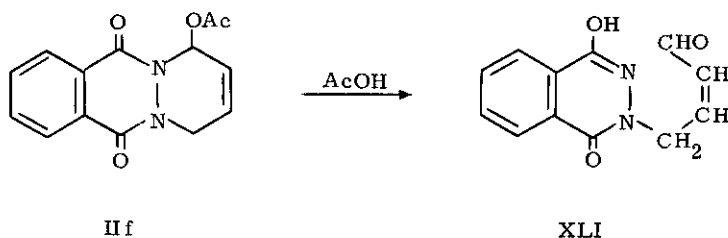
3.3 Ring opening reactions

Many of the adducts studied are affected by diluted acidic solutions, experimenting cleavage of N-C bond. When the hydrogenated adducts XVI-XX are treated with diluted sulphuric acid, the amido groups are readily hydrolyzed to give the corresponding dicarboxylic acids and very unstable aminic compounds, tentatively identified as bicyclic perhydrodiazines. Thus, phthalic acid and another compound, for which structure XL has been proposed, have been isolated in the hydrolysis of XIX²⁷.



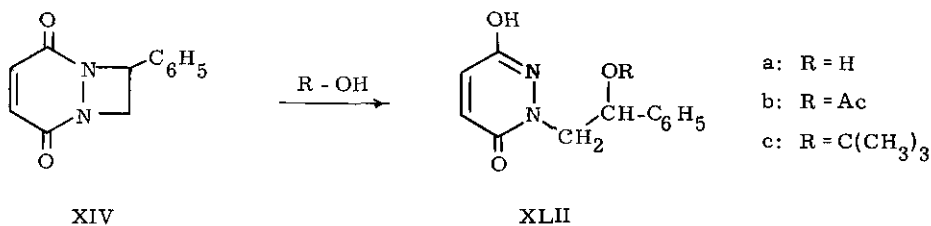
The cleavage of the N-alkyl linkage is much favored in those adducts with substituents attached to the carbon atoms adjacent to nitrogen^{7,8}. The acid treatment of IIh leads to phthalic hydrazide as the only recognizable product⁸. When the adduct obtained from phthalazine-1,4-dione and 1-acetoxybutadiene, IIi, is hydrolyzed with aqueous acetic acid, the expected 1-hydroxy

substituted compound cannot be isolated, because the tetrahydropyridazine ring is opened under the mild acidic conditions to give the corresponding α,β -unsaturated aldehyde, XLI⁷. These facts are in accordance with the previously mentioned influence of the substituents at C₁ over the



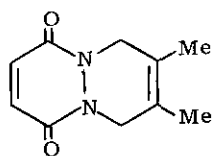
configuration of the ring, and the lengthening of the N-C₁ bond derived from it. On the other hand, if cleavage of the N-C bond proceeds via the formation of carbonium ions, the ring opening shall be more favored in the C₁-substituted adducts, from which more stable secondary carbonium ions can be formed, than in the unsubstituted ones.

The (2 + 2) cycloaddition products obtained from diazaquinones and styrene are extremely reactive, and undergo immediate opening of the four-membered ring with different reactants under very mild conditions. Thus, compound XIV adds water, acetic acid or tert-butanol to give respectively XLIIa, b or c¹³. As seen before, cleavage of the more substituted N-alkyl bond occurs.

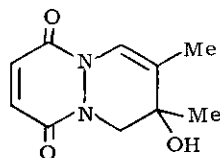
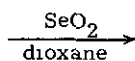


4. OXIDATION WITH SELENIUM DIOXIDE

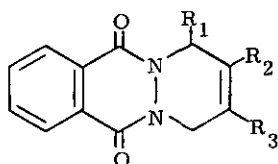
Selenium dioxide is a suitable reagent for the oxidation of carbon atoms attached to double bonds²⁸. Its reaction with adducts obtained from pyridazine-3,6-dione or phthalazine-1,4-dione and methyl substituted derivatives of butadiene affords different types of oxidation products, some of them involving isomerization of the double bond formed in the cycloaddition reaction⁷. In most cases the major reaction products are identified as hydroxylated derivatives of the isomerized adducts. For example, oxidation of Id and IIa, d, e leads to XLIII and XLIVa, d, e respectively, in yields oscillating between 30 and 50%. These results are consistent with the mentioned tendency of the adducts substituted at C₂ to experiment rearrangement of the double bond to the more conjugated 1,2-position.



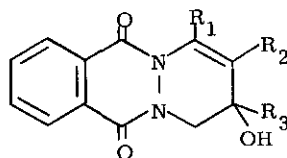
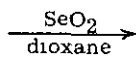
Id



XLIII



II



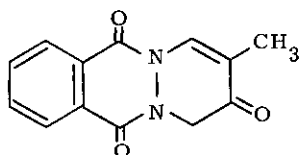
XLIV

a: $R_1 = R_3 = \text{Me}$; $R_2 = \text{H}$

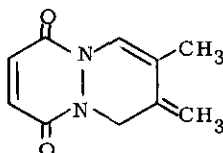
d: $R_1 = R_3 = \text{H}$; $R_2 = \text{Me}$

e: $R_1 = \text{H}$; $R_2 = R_3 = \text{Me}$

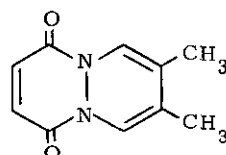
A variety of by-products have also been identified in these reactions. Thus, the keto derivative XLV has been isolated in a 25% yield during the oxidation of IId, and compounds XLVI and XLVII were formed by dehydration of Id in 25% and 15% yields.



XLV



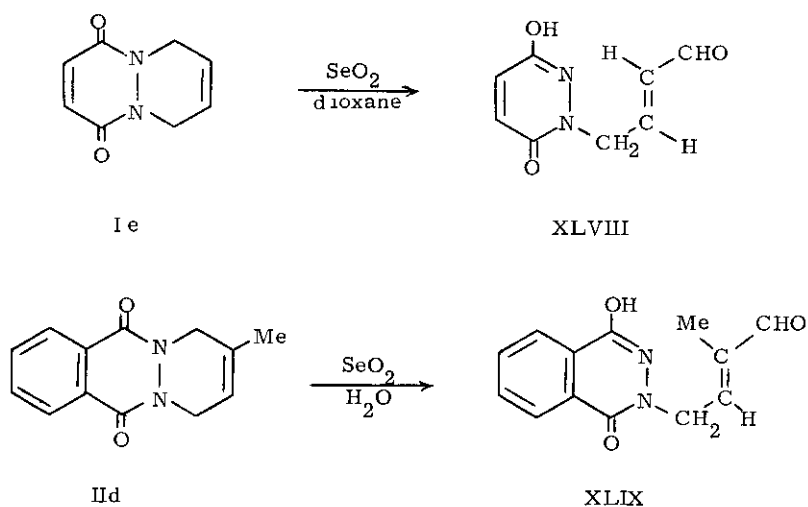
XLVI



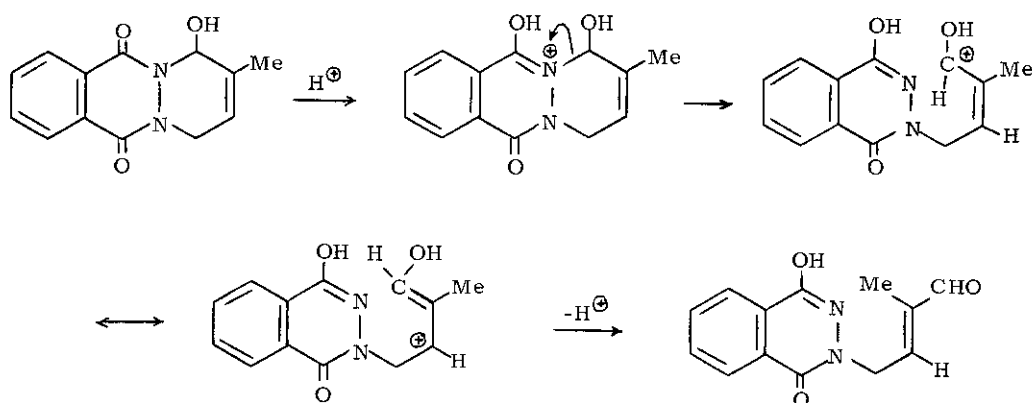
XLVII

As could be expected from arguments previously exposed, no isomerization of the double bond has been observed in the oxidation of unsubstituted adducts. Treatment of Ie with selenium dioxide under the same conditions employed in reactions described above affords the α,β -unsaturated aldehyde XLVIII by ring opening. From the coupling constant value measured in the NMR spectrum for the two ethylenic protons of this compound, a trans configuration has been assigned to the double bond⁶.

On the other hand, when the oxidation of adduct IId is performed in the presence of water, the corresponding α,β -unsaturated aldehyde XLIX is obtained as the major reaction product. The most suitable interpretation is that hydroxylation occurs in both cases on the carbon atom attached to nitrogen, and the hydroxylated derivatives undergo ready cleavage of the N-C bond, as has been shown to occur during the hydrolysis of the acetylated adduct IIc.



The mechanism depicted in scheme 3 has been proposed for this ring opening⁶.



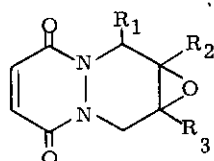
Scheme 3

5. EPOXIDATION AND FURTHER OPENING OF THE OXIRANE RING

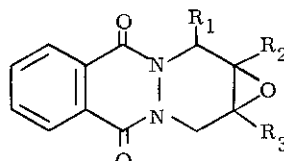
5.1 Epoxidation reactions

In order to introduce at the tetrahydropyridazine ring formed in the cycloaddition substituents capable of modifying the biological properties of the adducts, new derivatives have been prepared by epoxidation of the double bond and further electrophilic cleavage of the oxirane ring. Direct epoxidation of adducts with *m*-chloroperbenzoic acid takes place in most of the cases in good yields. Epoxides L to LIII have been obtained from the cycloaddition products of pyridazine-3,6-dione (La-d), phthalazine-1,4-dione (LIa-d), 5-hydroxyphthalazine-1,4-dione

(LIIIa), 5-chlorophthalazine-1,4-dione (LIIIb) and benzo(g)phthalazine-1,4-dione (LIIa-b), either with methylsubstituted 1,3-butadienes or 1,2-dimethylenecyclohexane^{4,10}.



L



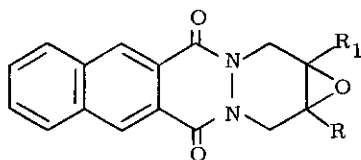
LI

a: $R_1 = R_3 = \text{Me}$; $R_2 = \text{H}$

b: $R_1 = R_2 = \text{Me}$; $R_3 = \text{H}$

c: $R_1 = R_3 = \text{H}$, $R_2 = \text{Me}$

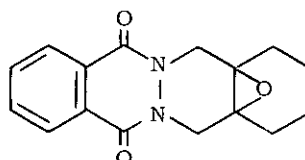
d: $R_1 = \text{H}$; $R_2 = R_3 = \text{Me}$



LII

a: $R_1 = \text{Me}$; $R_2 = \text{H}$

b: $R_1 = R_2 = \text{Me}$

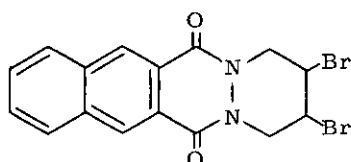


LIII

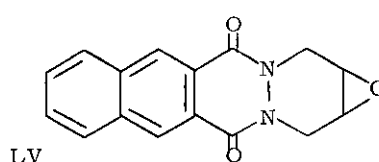
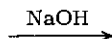
a: $R = \text{OH}$

b: $R = \text{Cl}$

In the epoxidation of the 4a, 8a-diazabicyclic adducts, only the more activated double bond results affected. On the other hand, no reaction is observed in adducts which lack electron-donating methyl groups attached to the double bond, even under stronger reaction conditions. The desactivating action of the two withdrawing amido groups is so strong that the presence of donating substituents is required in order that the epoxidation can be achieved. However, the non-substituted epoxides can be obtained by dehydrobromination of the corresponding bromohydrins (formed by NBS treatment of the adducts, see later) in the presence of aqueous sodium hydroxide. Thus, epoxide LV is prepared from the corresponding butadiene adduct in 78% yield. Extremely mild conditions are required in this reaction, because of the great tendency of the amido group to undergo hydrolysis in the aqueous basic medium employed.

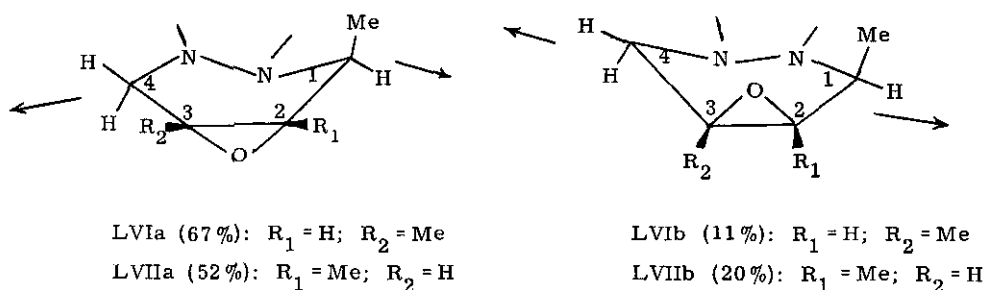


LIV



LV

The epoxidation reactions afford either a single product or a mixture of cis and trans isomers, according to the location of the substituents in the piperidine ring. By epoxidation of adducts IIa and IIb, the corresponding two pairs of diastereomers LVIIa-b and LVIIIa-b are formed in yields shown in scheme 4⁴. Their configurations have been unambiguously established both by X-ray diffraction and NMR techniques^{4, 29, 30}. In these epoxides, the nitrogen atoms are close to a sp^2 hybridization, with a quasi-planar geometry. Isomer LVIIa exhibits a quasi-1,3-diplanar conformation, intermediate between sofa and boat, with two zero torsional angles, namely $C_1-C_2-C_3-C_4$ and C_3-C_4-N-N . In it, the methine at C_1 is consistently more deviated from the plane of the benzo and central rings than in the opposite methylene. The C_1 methyl group shows a trans orientation with respect to the oxiranic oxygen.



Scheme 4

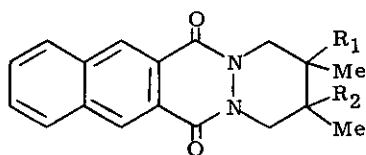
Isomer LVIIb has a 1,2-diplanar conformation, in which the zero torsional angles are $N-C_1-C_2-C_3$ and $C_1-C_2-C_3-C_4$, and consequently the methine at C_1 is nearly coplanar to the central ring. The C_1 methyl group and the oxiranic oxygen are in a cis relation. Owing to these variations, the relative positions of the $C=O$ groups (shown by arrows in scheme 4) regarding the substituents at C_1 and C_4 are consistently different in both stereoisomers. This is an interesting fact, because it provides a method for differentiating the type of isomer on the basis of data obtained from its NMR spectrum. The more or less proximity of hydrogen atoms or substituents attached to C_1 and C_4 regarding the deshielding plane of the $C=O$ groups significantly affects their chemical shift values, allowing the identification of the respective isomer. Results obtained from isomers LVIIIa and LVIIIb are analogous to those exposed above. In the synthesis of the 4a, 8a-diazabicyclic epoxides La and Lb, only the major trans isomers (referred to the relative dispositions of the C_1 -Me and the epoxidic oxygen) are isolated, although the formation of the other isomers has been detected.

As can be seen from all these reactions, the major isomer is that showing a trans configuration. This fact is in good agreement with the high stereoselectivity found usually in epoxidations, since the peracid attack takes place primarily at the less hindered side of the double bond, to give as the main product the epoxide with the less steric hindrance³¹.

5.2 Oxirane ring opening reactions

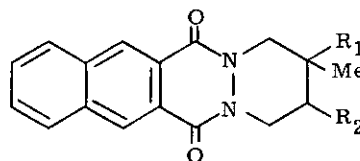
Addition reactions in acidic media have been performed on the oxirane ring of the epoxidated adducts. By treatment of the epoxides with dimethyl sulphoxide containing the boron trifluoride-etherate complex, followed by hydrolysis of the intermediate sulphoxonium salts, the corresponding 1,2-diols are formed in 50-60% yields³². In some cases, this opening has also been accomplished with aqueous sulphuric acid in acetone solution^{6, 18}. Reaction of the epoxides with hydrogen bromide in methanol affords the expected bromohydrins³².

A wide NMR study has been performed on the stereochemistry of these products in the opening reactions of unsubstituted, 2-methyl- and 2,3-dimethyl-substituted 2,3-epoxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-diones³² and, in search of more NMR data, the corresponding trans-dibromides and acetylated derivatives have also been prepared, for comparison (compounds LVIII a LX). The effect of solvent change upon the chemical shifts of the terminal piperidazine ring protons has been measured and discussed for deuterated chloroform, deuterated dimethyl sulphoxide and trifluoroacetic acid. Evidence for the stereochemistry



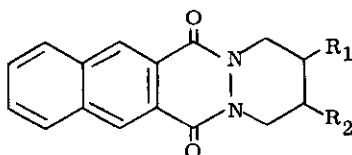
LVIII

- a: $R_1 = R_2 = \text{OH}$
- b: $R_1 = \text{Br}; R_2 = \text{OH}$
- c: $R_1 = R_2 = \text{Br}$
- d: $R_1 = \text{Br}; R_2 = \text{OAc}$
- e: $R_1 = R_2 = \text{OAc}$



LIX

- a: $R_1 = R_2 = \text{OH}$
- b: $R_1 = R_2 = \text{Br}$
- c: $R_1 = R_2 = \text{OAc}$



LX

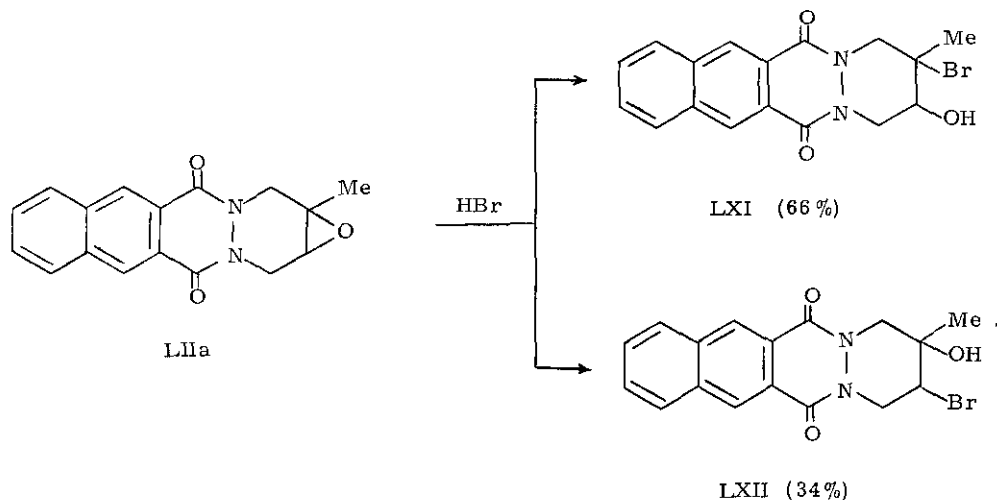
- a: $R_1 = R_2 = \text{OH}$
- b: $R_1 = \text{Br}; R_2 = \text{OH}$
- c: $R_1 = R_2 = \text{Br}$
- d: $R_1 = \text{Br}; R_2 = \text{OAc}$

of the hydroxy groups has been obtained from the acetylation downfield shift effect³³ shown by the adjacent equatorial hydrogens. In all the brominated derivatives, 1,3-syn-diaxial interactions between the bromine atoms and protons of the piperidazine ring are observed, but they are not significant in the case of the other substituents. Effects of the different substituents on the chemical shifts of the piperidazine ring protons have been evaluated in compounds LVIII and LIX, and the following empirical rules enable the calculation of the position of the different hydrogens

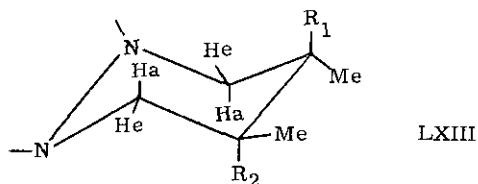
in the spectra:

- Deshielding influence due to an acetoxy group: + 0.8 - 1.0 ppm on the vicinal equatorial proton, negligible on the axial proton.
- Inductive effect due to a bromine atom: + 0.2 - 0.3 ppm on the adjacent methylene group, negligible on the other methylene.
- Spatial interaction due to an axial bromine: + 0.2 ppm on the proton in a 1,3-axial arrangement.

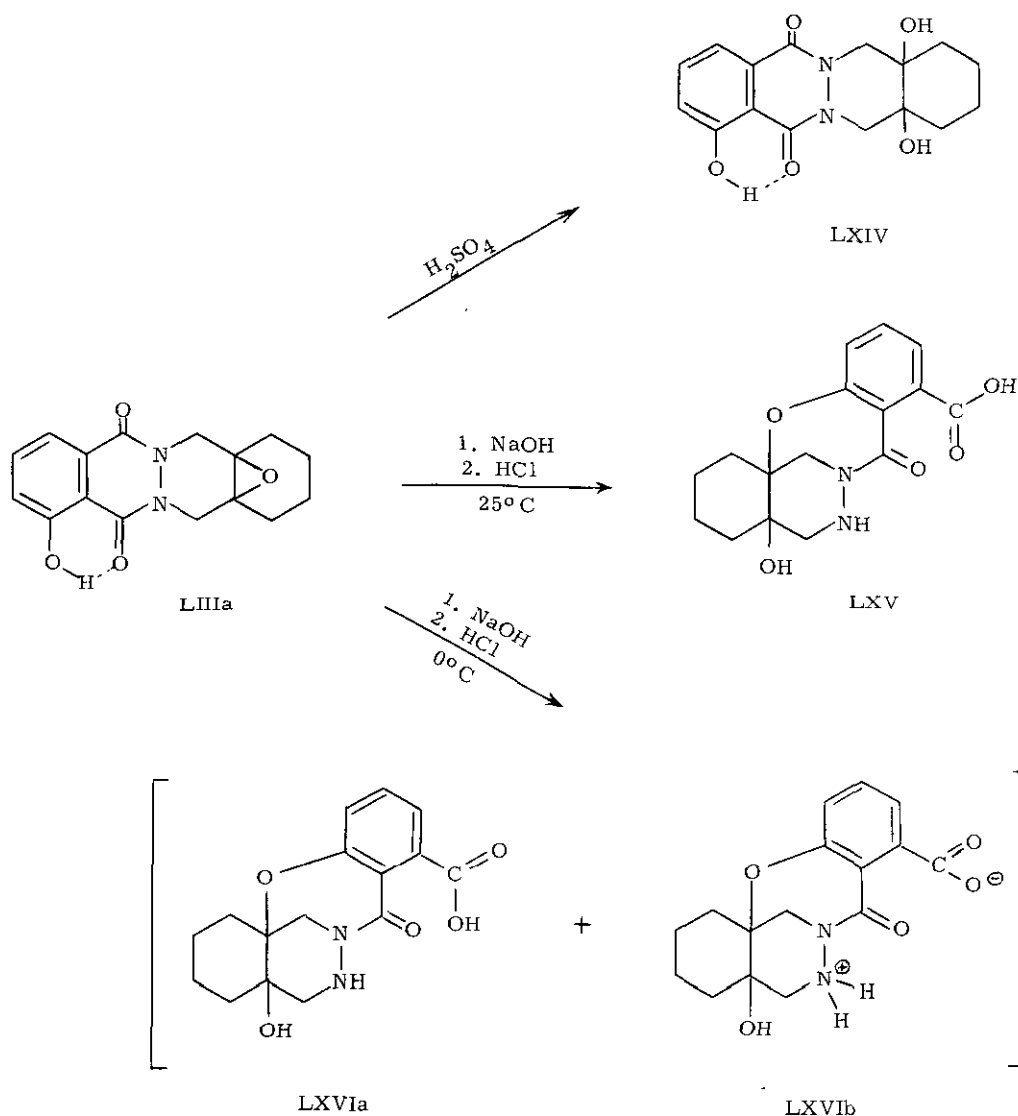
From the NMR study and also on the basis of X-ray diffraction data³⁴, it can be deduced that these reactions proceed in a stereospecific way, and the Furst-Plattner rule of 1,2-transdiaxial ring-opening is obeyed. When the oxirane ring is unsymmetrically substituted and the reactant is also unsymmetrical, the expected isomers are obtained, in ratios according to the usual regioselectivity in the opening of epoxides, the major product always corresponding to an attack of the electrophile at the more substituted carbon atom of the ring. For example, the two isomeric bromohydrins LXI and LXII are formed from LIIa in respective yields of 66 and 34%¹⁷.



The configuration of the terminal piperidazine ring in the LVIIIa-e derivatives closely approaches to a chair form like LXIII, with both methyl groups in a trans-equatorial orientation, and intermolecular hydrogen bondings have been found between the carbonyl oxygen atoms and the hydroxy groups³⁴. Nevertheless, when one methyl group is substituted by hydrogen in LIXa-c, the steric requirements are less strict, the distorting effect of the amido groups predominates, and the planarity of the ring increases as it moves away from the chair form. Hence, the axial



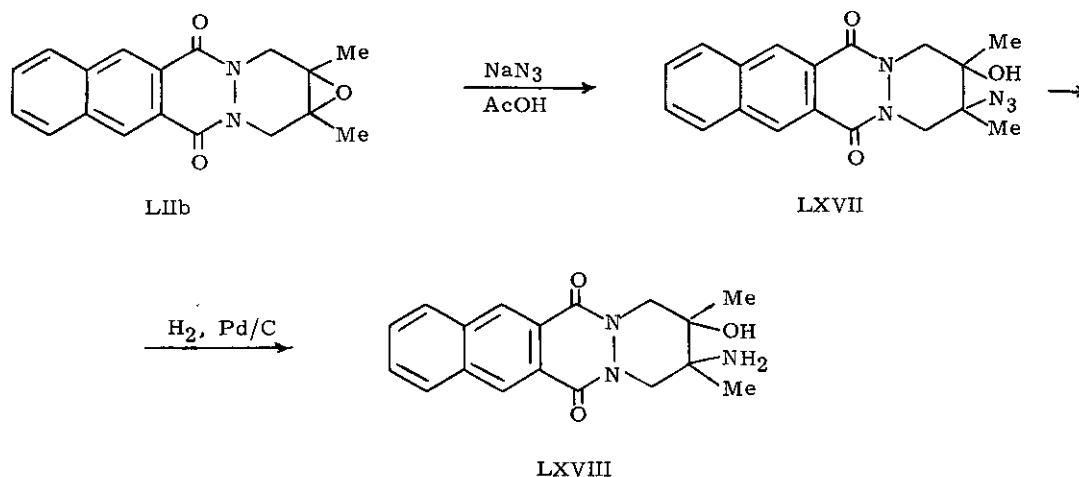
methylenic protons come nearer to the amidic C=O groups, while the corresponding equatorial ones move slightly away. Finally, most of the less highly substituted derivatives LX have been shown to be in some kind of conformational equilibrium as solutes, possibly through nitrogen inversion, as it is usual in substitute piperidazines¹⁹⁻²¹. This different behaviour is illustrated by the equivalence shown by axial and equatorial protons at room temperature, and may be explained by considering that the steric and energetic requirements for the equilibrium must be diminished when the number of substituents attached to the piperidazine ring decreases. In fact, evidence for conformational equilibrium has also been obtained in some cases in trisubstituted derivatives like LIX (for example, in the isomeric bromohydrins LXI and LXII³⁵), but never in any of the tetrasubstituted derivatives.



It is interesting to point out the results obtained in the opening of epoxide LIIIa. By treatment with aqueous sulphuric acid, the expected 1,2-diol, LXIV, is formed in 80% yield, but reaction in alkaline aqueous solution results in opening of the pyridazinedione ring, yielding an intermediate sodium salt which in acidic medium is transformed into a new 1,4-oxazepine³⁶ derivative, this compound being isolated in different crystalline forms LXV, LXVIa and LXVIb.

The form LXV is obtained when the sodium salt solution is neutralized at room temp. and forms LXVIa-b are identified when the neutralization process is performed at 0°C. From the X-ray diffraction analysis it can be derived that the main difference between LXV and LXVI is the orientation adopted by the carboxylic group³⁷. In compound LXVI, 50% of the molecules are ionized forming "zwitterions". In all cases, the 1,4-oxazepinone and the perhydrophthalazine rings adopt the twisted boat and the perhydrophthalazine rings adopt the twisted boat and chair conformations respectively, being the hydroxy group in an axial orientation. Both nitrogen atoms are pyramidal. Several types of intermolecular hydrogen interactions have been found and studied both in LXV and LXVI^{36, 37}. Formation of these compounds from LIIIa could be explained via an ionic mechanism involving nucleophilic attack of the phenoxide anion in the alkaline medium.

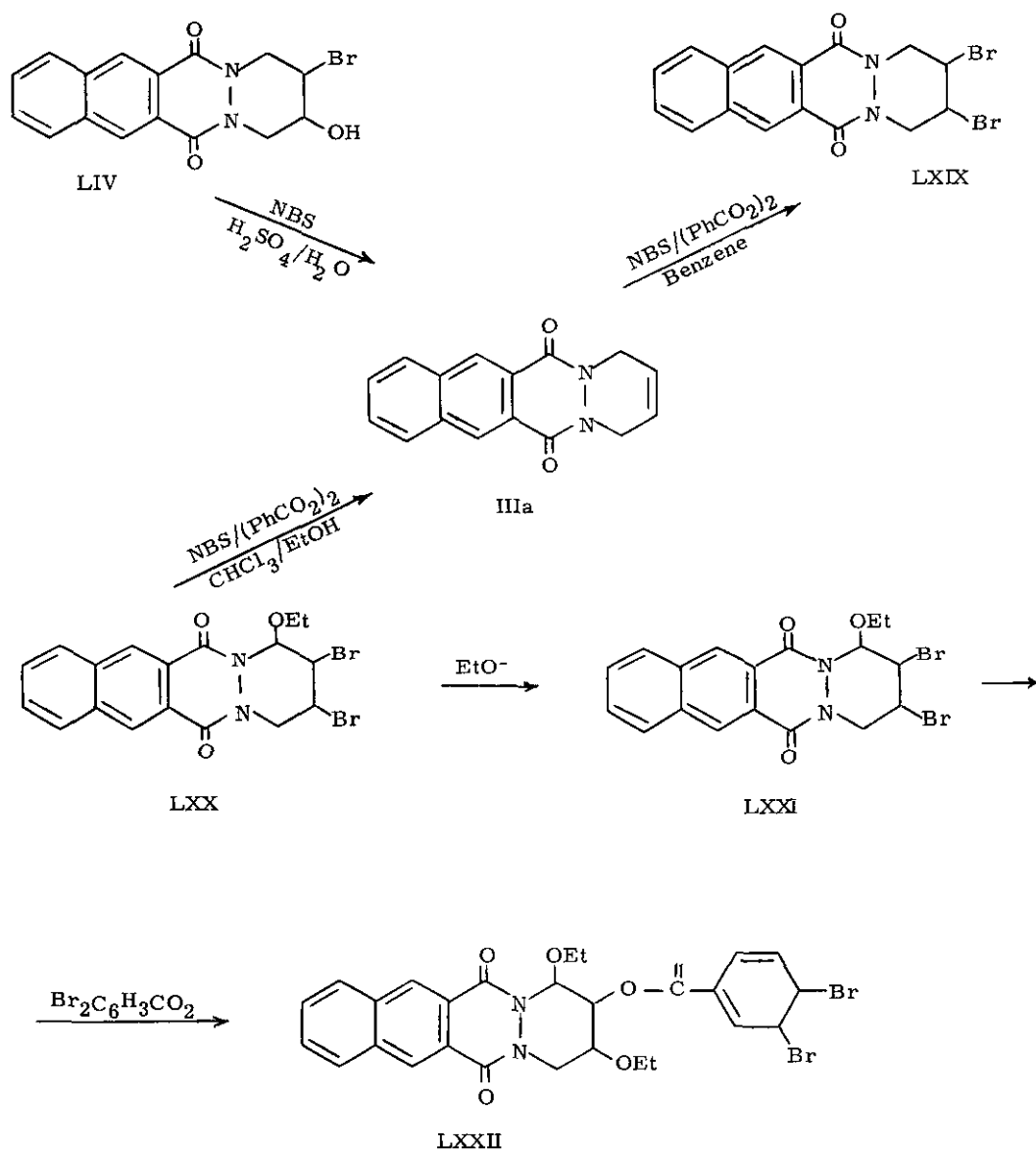
In addition to the above described oxirane ring-opening reactions, essays with other reactants have been performed. Thus, treatment of the epoxides with sodium azide in acetic acid leads to the corresponding hydroxyazides, hydrogenation of which over palladium on charcoal gives hydroxyamines like LXVIII³⁵. Different opening products have also been identified in the presence of ethanol or sodium ethoxide³⁵.



6. REACTIONS WITH N-BROMOSUCCINIMIDE

The action of N-bromosuccinimide (NBS) on adducts obtained from benzo(g)phthalazine-1,4-dione and methyl substituted butadienes has been studied⁹. This reaction has been shown to be very sensitive to the experimental conditions employed, different adduct derivatives resulting depending on the media in which the reaction is carried out.

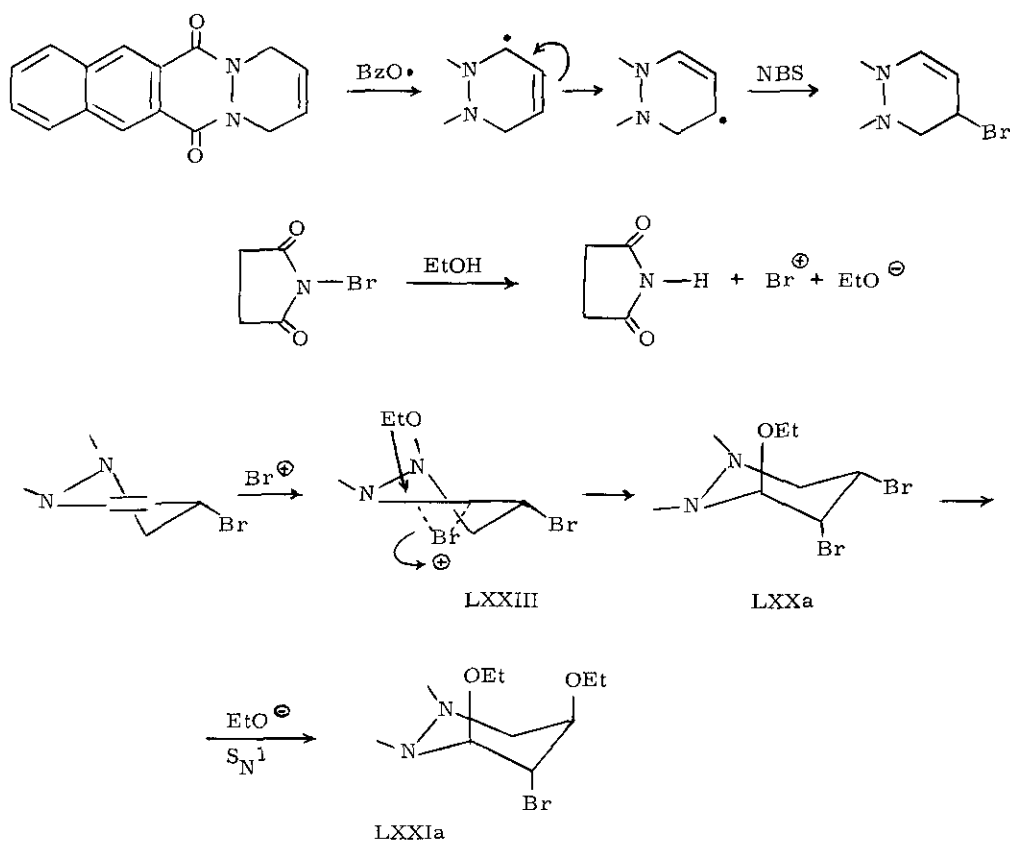
Scheme 5 summarizes the different possibilities for the adduct of benzo(g)phthalazine-1,4-dione with butadiene IIIa. When the NBS reaction is performed in an aqueous suspension containing some drops of sulphuric acid, bromohydrin LIV is formed in almost quantitative yield, as expected. In benzene solution containing a catalytical amount of benzoyl peroxide, the dibrominated derivative LXXIX is obtained. In fact, conditions employed are strongly favorable to a free radical mechanism and, consequently, allylic bromination should take place. However, the withdrawing effect of the two carbonyl groups destabilize the allylic free radical, and addition to the double bond is favored.



Scheme 5

Treatment of IIIa with NBS in chloroform containing 1% ethanol and a catalytical amount of benzoyl peroxide affords LXX in 41% yield, but when longer reaction times are employed, a mixture of compounds LXX, LXXI and LXXII is isolated, in 32, 20 and 5% yields respectively. The stereochemistry of the terminal piperidine ring has been resolved in LXX and LXXI by studying their NMR spectra. In compound LXX, the ethoxyl group at C₁ and the adjacent bromine are in an axial-axial relationship, whereas the second bromine is equatorially oriented (LXXa). Compound LXXI exhibits the same trans-diaxial orientation of the ethoxyl group at C₁ and the bromine atom at C₂, but the new ethoxyl group has an axial disposition (LXXIa), in opposition with that equatorial of the bromine atom in LXXa.

The stereochemical features found in these derivatives suggest the mechanism depicted in scheme 6 for their formation. In a first step an allylic bromination takes place, with



Scheme 6

rearrangement of the allylic radical intermediate to a more stable one, owing to conjugation established through the lone pair of the adjacent nitrogen atom (in accordance with the tendency of these adducts to isomerize in acidic medium, see section 3.1). After that, trans-diaxial addition

of bromine and ethoxyl to the new double bond formed occurs. On the other hand, it seems that LXXI and LXXII are formed from LXX by successive substitutions of the two bromine atoms by a second ethoxyl group and dibromobenzoate produced in the bromination with NBS of the benzoyl peroxide used as catalyst. The different orientation of substituents at C₃ in both LXX and LXXI is consistent with the formation of LXXI by S_N¹ reaction of the bromine atom in LXX, with configurational inversion at C₃. Such a phenomenon would be favored by the unstability of the intermediate carbonium ion.

A remarkable fact is that LXX is obtained via the cis-epibromonium ion LXXIII (less stable than the trans one), in opposition to what could be expected if the usual mechanism of addition reactions was followed. This behaviour is not exclusive for compound LXX, and the same pattern is observed in the NBS reactions performed on the double bond of adducts substituted at different positions of the terminal piperidine ring³⁵. The apparently anomalous regio- and stereoselectivity found in the NBS/ROH additions to these compounds is now being investigated, but sufficient evidence is already available for the existence of a mechanism in which the electrophilic step is reversible, and the regio- and stereoselectivity are determined during the nucleophilic step, which is the rate-limiting one. Therefore, a syn-stereoselectivity should be expected for the attack by the electrophilic bromine, to give preferably the less stable but more reactive cis-epibromonium ion. This mechanism has been recently demonstrated to occur in additions of N-bromoamides to cyclohexenes and some heterocyclic analogs^{38,39}.

Finally, direct regiospecific addition of the N-bromosuccinimide molecule to give α,β -bromosuccinimido derivatives, has also been observed in adducts whose double bond is specially deactivated²⁵.

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